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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/762,566	01/23/2004	Richard Franklin	20342/1202529-US1	3220

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DARBY & DARBY P.C.
P.O. BOX 770
Church Street Station
New York, NY 10008-0770

EXAMINER	
HUGHES, ALICIA R	
ART UNIT	PAPER NUMBER
1614	
MAIL DATE	DELIVERY MODE
12/10/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/762,566	FRANKLIN, RICHARD	
	Examiner	Art Unit	
	ALICIA R. HUGHES	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 July 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,12,13 and 17-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,12,13 and 17-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2 sheets*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

Claims 2, 12-13 and 17-22 are pending. Applicants cancelled claims 3, 6-9, 14, 15, 24-25, 29, 31, 33-34, 36 and 50 in their response dated 31 July 2009.

Applicants' arguments, filed on 31 July 2009, have been fully considered and are deemed to be persuasive regarding the previous rejection. Rejections and objections not reiterated from previous Office Actions are hereby withdrawn.

Upon reconsideration of the pending claims, as presented, the following new rejections are applied. They constitute the complete set of rejections being applied to the instant application presently.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Objection to the Specification

The disclosure is objected to because of the following informalities: the anagrelide chemical structure in the specification at the top of page 31 is missing a double bond in the central ring therein. Appropriate correction is required.

Claim Rejections - 35 U.S.C. §112.1

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person

> skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2, 12-13 and 17-22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant, in its Remarks filed on 31 July 2009, amended claim 2 to include a series of previously unincluded steps, such as "minimizing the amount of first pass liver metabolism of the anagrelide to 3-hydroxy anagrelide in the transdermally administered patient compared to the amount of the first pass liver metabolism of an equivalent amount of anagrelide orally administered to a patient" an "reducing the amount of phosphodiesterase-III (PDEIII) inhibition by 3-hydroxy anagrelide in the transdermally administered patient compared to the amount of PDEIII inhibition by 3-hydroxy anagrelide in a patient orally administered an equivalent of anagrelide" and as well, "reducing the cardiovascular side effects caused by PDEIII inhibition in the transdermally administered patient compared to the cardiovascular side effects in a patient "rarely administered an equivalent amount of anagrelide" (Amendment to the Claims dated 31 July 2009, Claim 2).

These amendments change the scope of the claims and originally filed and a review of specification, as filed, does not disclose the invention embodied by the present set of claims. The Examiner does appreciate the Applicant's efforts to point to page and line numbers that

might support the new amendments. However, in taking the time to make a careful review of the referenced pages and lines, the correlation needed to support the amendments was not found.

This is a new matter rejection.

Claims 2, 12-13 and 17-22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant, in its Remarks filed on 31 July 2009, amended claim 2 to include "minimizing the amount of first pass liver metabolism of the anagrelide to 3-hydroxy anagrelide in the transdermally administered patient compared to the amount of first pass liver metabolism of an equivalent amount of anagrelide orally administered to a patient (Amendment to the Claims dated 31 July 2009, Claim 2). However, Applicant has failed to disclose what amount of a skin-permeable form of anagrelide would be administered to minimize the amount of the first pass liver metabolism of the anagrelide to 3-hydroxy anagrelide as required form the practice of claim 2, part b.

Claim Rejections – 35 U.S.C. §103

I. First 103 Rejection

Claims 2, 12, 17-20 and 50 are rejected under 35 U.S.C. 103(a) as being obvious over U.S. Patent No. 6,194,420 [hereinafter referred to as "Lang"], in view of U.S. Patent No. 6,221,383 [hereinafter referred to as "Miranda et al"], and in further view of U.S. Patent No.

6,024,975 [hereinafter referred to as "D'Angelo et al"] and in further view of Solberg, Lawrence, "Therapeutic Options for Essential Thrombocythemia and Polyctyhemia Vera, *Seminars in Oncology*, Vol. 28, Issue 3, Supplement 10, page 10-15 (2002)[hereinafter referred to as "Solberg"] as evidenced by Bonkovsky, Herbert L., et al, "Drug-Induced Liver Injury," *Zakim and Boyer's Hepatology, 5th Edition, pages 503-550* (2006)[hereinafter referred to as "Bonkovsky et al"] and Ammar, H.O. et al, "Design of a Transdermal Delivery System for Aspirin as an Antithrombitic Drug," *International Journal of Pharmaceutics*, Vol. 327, pages 81-88 (2006)[hereinafter referred to as "Ammar et al"].

The Applicant now argues that there are unexpected results that render the instant invention non-obvious and cites the declaration of Dr. Richard Franklin to support the premise that Applicant has unexpectedly discovered that transdermally administering anagrelide to treat thrombocythemia minimizes the adverse cardiovascular side effects observed when anagrelide is administered orally. The Applicant has also added a number of new limitations to independent claim 2.

The teachings of Lang, Miranda, and D'Angelo as set forth in this Office's Action dated 19 April 2007, 16 April 2008, 17 November 2008 and 01 April 2009 are incorporated herein by reference and for the reasons set forth therein are applied to the same claims presently and in entirety.

Solberg teaches that aspirin, like anagrelide, is useful in the treatment of thrombocythemia (Solberg, Jr., page 11, chart and Col. 2 through page 12, Col. 1 and chart on pages 12 and 13) and there is a correlation between the treatment of thrombocythemia with aspirin and anagrelide and aggravation of cardiovascular risk factors that the literature does seek

to solve (Solberg, Jr. at Page 15, Col. 1). Furthermore, the prior art appreciates the use of drugs transdermally to treat antithrombotic conditions (Ammar et al Abstract and pages 86 and 87 in their entirety).

It is well-known in the pharmaceutical art that most chemicals are ingested orally and absorbed primarily in the small intestine with some undergoing initial metabolism within the gastrointestinal tract. *See* Bonkovsky, Page 503, Col. 1, specifically. However, it is not in these places but rather when compounds and/or metabolites enter the splanchnic blood where they are eventually delivered via portal circulation to the liver, that we have the effect of first pass metabolism (where bioavailability is most important). *Id.*

Transdermal delivery of drugs generally enable with immediacy pass of the first liver metabolism, bypassing the GI tract and small intestine and increasing bioavailability while at the same time decreasing various side effects. *Please see*, e.g., Ammar, H.O. et al, "Design of a Transdermal Delivery System for Aspirin as an Antithrombitic Drug" *at* page 87 Col. 2. Further, orally administered drugs, particularly aspirin and others known to treat thrombocythemia, require high and frequent dosing because they undergo extensive presystemic hydrolysis in the gut and liver. *Id.* As a result of the teachings of Anmar given the state of the art generally regarding the transdermal delivery of drugs, in the absence of express evidence to the contrary, transdermal administration of the same reduces this extensive presystemic hydrolysis resultant from oral administration, provides enhanced bioavailability and as appreciated in the art, reduces cardiovascular and gastrointestinal side effects. *Please see, e.g.*, Anmar et al at page 87, Col. 2.

Finally, there are a number of new limitations recited in Applicant's claim 2. In the absence of express evidence to the contrary, these limitations are no more than the results of administration of the drug of the instant invention discoverable through routine means by those of ordinary skill in the art.

In light of the foregoing, it would have been *prima facie* obvious to one of ordinary skill in the art to combine the teachings of Lang, Miranda et al, and D'Angelo to conclude that the combination of anagrelide or its salt form, along with a skin permeation enhancer, administered transdermally so as to avoid the first pass liver metabolism would be effective in the treatment of essential thromboycythemia.

Furthermore, it would have been *prima facie* obvious to one of ordinary skill in the art that the administration of a single or multiple layer formulation of an effective amount of anagrelide or an anagrelide salt and a menthol acting has a skin permeation enhancer with acrylic adhesive with a surface area ranging from 1 to 200 square centimeters acting together as a transdermal delivery device would be effective for treating essential thrombocythemia.

Accordingly, for the above reasons, the claims are deemed properly rejected.

II. Second 103 Rejection

Claims 21-22 are rejected under 35 U.S.C. 103(a) as being obvious over Lang in view of D'Angelo and in further view of U.S. Patent No. 5,133,972 [hereinafter referred to as "Ferrini et al"].

The Applicant now argues that there are unexpected results that render the instant invention non-obvious and cites the declaration of Dr. Richard Franklin to support the premise that Applicant has unexpectedly discovered that transdermally administering anagrelide to treat

thrombocythemia minimizes the adverse cardiovascular side effects observed when anagrelide is administered orally.

The teachings of Lang and D'Angelo et al, *supra* and as stated in this Office's Actions of 19 April 2007, 16 April 2008, 17 November 2008 and 01 April 2009 as well as the arguments herein, *supra*, are incorporated herein by reference, in total. The teachings of Ferrini et al, as noted in this Office's previous actions are incorporated herein by reference in total, also.

The teachings of Bonkovsky et al, Ammar et al and Solberg, *supra*, are incorporated herein by reference in their entirety, also. In light of the foregoing and for the reasons made previously of record, the claims are deemed properly rejected.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alicia Hughes whose telephone number is 571-272-6026. The examiner can normally be reached from 9:00 A.M. until 5:00 P.M. on Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, can be reached at 571-272-0718. The fax number for the organization where this application is proceeding is assigned 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For information about the PAIR system, see

http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Alicia R. Hughes/
Examiner, Art Unit 1614

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614